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(57) Abstract

Administration of retinoids by inhalation is used to overcome the chronic toxicity problems presented by systemic administration and to make retinoid therapy available as an option for the prevention of epithelial cancers of the respiratory tract, especially those that are associated with tobacco use. Retinoids are administered by inhalation to the respiratory tract of the individual as an air-borne composition with a metered dose aerosol-producing inhaler, in which the retinoid is dissolved in a combination of a pharmaceutically acceptable chlorofluorocarbon propellant and an alkylamine solubilizing agent.

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USE OF INHALED RETINOIDS IN THE PREVENTION OF CANCER

DESCRIPTION

BACKGROUND OF THE INVENTION

Retinoids are a class of naturally occurring and synthetic derivatives of Vitamin A which function *in vivo* as regulators of a number of physiological functions including cellular proliferation, cytodifferentiation and embryonal morphogenesis. This class includes a number of clinically important compounds such as those shown Fig. 1 which have been shown or hypothesized to have utility in the therapy and prevention of various types of cancer. For example, Hong et al., N. Eng. J. Med. 323: 795-801 (1990) have shown that adjuvant treatment with 13-*cis* retinoic acid after definitive anti-cancer treatment in patients with carcinoma of the head and neck significantly reduces the incidence of secondary tumors of the aerodigestive tract. Head and neck cancer, like lung cancer, is significantly related to tobacco smoking, and in fact many of the tumors reduced in incidence in the Hong et al. study were lung cancers. Retinoids have also been shown to be effective in the prevention and reversal of certain types of induced hyperplasia and metaplasia in cultured rodent respiratory epithelial. Lasnitzki et al., Cancer Treatment Reports 66: 1375-1380 (1982).

Unfortunately, while retinoids have been shown to provide beneficial effects in the prevention of at least some types of cancer, the therapeutic regiment requires chronic administration. Under these circumstances, substantial systemic toxicity may result, including hyperlipidemia, hypercalcemia, and skin, liver and central nervous system toxicity. This toxicity has limited the utility of retinoids as therapeutic agents in the prevention of cancer.

SUMMARY OF THE INVENTION

We have now developed a system for administration of retinoids by inhalation to overcome the chronic toxicity problems presented by systemic administration and to make retinoid therapy available as an option for the prevention of epithelial cancers of the respiratory tract, especially those that are associated with tobacco use. Thus, in accordance with the present invention, there is provided a method for prevention of epithelial cancer

of the respiratory tract in an at-risk individual, comprising administering by inhalation to the respiratory tract of the individual an air-borne composition (i.e., an aerosol or finely divided dry powder) comprising a therapeutically effective amount of at least one retinoid. The retinoid is suitably administered with a metered dose aerosol producing inhaler, in which the retinoid is dissolved in a combination of a pharmaceutically acceptable chlorofluorocarbon propellant and an amine solubilizing agent.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 shows the structures of various clinically significant retinoids;

Fig. 2 shows an inhaler in accordance with the invention;

Figs 3A and B show plasma and liver levels of all-*trans* retinoic aicd after administration to rats using three different routes; and

Fig. 4 shows lung tissue levels of all-*trans* retinoic aicd after administration to rats using three different routes.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to the prevention of epithelial cancer of the respiratory tract in an at-risk individual by administering by inhalation to the respiratory tract of the individual an aerosol comprising a therapeutically effective amount of at least one retinoid. The method provides delivery of the pharmaceutically active retinoid directly to the affected areas, thus increasing bioavailability and decreasing systemic toxicity. It will be recognized by persons skilled in the art that "prevention" of cancer is difficult to prove in the absolute sense because one cannot predict with certitude what will transpire in the future. Thus, as used in the specification and claims of this application, the terms "prevention" or "preventing" refer to a reduction of the risk of contracting epithelial cancer, or to a delay in the onset of epithelial cancer.

Inhalation of pharmaceutically-active compositions is not a new concept, and various compounds used in asthma therapy and the like have been administered in this manner. Commonly, however, such aerosols are formed from the active compounds solubilized in water. However, most retinoids of clinical interest, including all of the "natural retinoids" such as all-*trans* retinoic acid, 13-*cis* retinoic acid and 9-*cis* retinoic acid, are highly

lipophilic and thus very insoluble in water. For this reason, conventional water-based formulations cannot be used for aerosol administration of these compounds. To make it possible to perform inhalation therapy using retinoids, it was therefore necessary to define a solvent system which (1) solubilized sufficient amounts of the retinoids to provide a pharmaceutically-useful dosage, i.e., from about 0.1 to 5.0 mg/ml; (2) provided a retinoid solution of sufficient stability to permit distribution of a product; and (3) was substantially non-toxic in the amounts administered and thus suitable for administration to living patients.

Working towards this goal, we first looked at organic solvents. In the course of this investigation, we found that retinoids were only slightly soluble in ethanol or ethyl acetate. Methylene chloride or chloroform provided adequate solubilization, but the potential toxicity of these materials argued against their use as carriers in an aerosol for use in inhalation therapy.

Next, because of a report that the solubility of retinol (vitamin A) in water could be increased by addition of modified beta cyclodextrin (MOLECUSOL®), we next tried to prepare aqueous solutions of all-*trans* retinoic acid using MOLECUSOL® to enhance the solubility. Solutions containing 45% MOLECUSOL® did in fact enhance the solubility of the all-*trans* retinoic acid to a useful level, but the resulting solution had a thick, syrupy consistency which was unsuited for use in the generation of an aerosol. Similarly, efforts to solubilize all-*trans* retinoic acid in aqueous solution using phosphatidylcholine and phosphatidylethanolamine produced a viscous colloid which was unsuited for aerosol administration.

We next tried to use salts of the retinoids to obtain a water-soluble product for aerosol generation. When all-*trans* retinoic acid is treated with ammonium hydroxide, a water-soluble ammonium salt is obtained. The pH of solutions of this salt is too high (pH >10), however, for direct administration as an aerosol. Neutralization of the solution after dissolution of the retinoid led to the formation of a precipitate, both in the presence and absence of added beta cyclodextrin. Thus, the approach also failed to produce an acceptable solution for use in generating an aerosol.

Because of the solubility of all-*trans* retinoic acid in halogenated hydrocarbon solvents, we next considered the solubility of retinoids in various chlorofluorocarbon

propellants which have been used to deliver aerosolized solutions of other pharmaceutically-active compounds. All-*trans* retinoic acid was found to be only slightly soluble (about 0.1 mg/ml) in 1,1,2-trichlorofluoroethane and only slightly more soluble (2 mg/ml) in 2,2-dichloro-1,1,1-trifluoroethane (HCFC-123). Thus, as an initial matter, it did not appear that these solvents would be useful for producing useful solutions of retinoids for inhalation use.

Surprisingly, however, we found that the solubility of retinoids in chlorofluorocarbon solvents could be significantly increased by the addition of alkylamines, particularly secondary, tertiary and quaternary alkylamines having alkyl groups containing from 2 to 8 carbon atoms such as trioctylamine, spermine, triethylamine or tetramethylammonium bromide, and that the resulting solutions were stable for periods of 5 days or longer, and can be solubilized by shaking. Thus, one aspect of the present invention is a solution comprising a retinoid, a chlorofluorocarbon solvent, for example HCFC-123, HCFC-134A or HCFC-227, and an alkylamine which is effective to solubilize the retinoid in the chlorofluorocarbon solvent. The solution preferably contains from 0.1 to 10 mg of the retinoid and 0.1 to 5 mg of the alkylamine, more preferably 1 to 2 mg of the retinoid and 0.1 to 0.5 mg of the alkylamine, per ml of solution.

Retinoids useful in the present invention include the "natural retinoids" as well as pharmaceutically acceptable salts and esters thereof. Retinoids of particular interest in the present invention are all-*trans* retinoic acid, 13-*cis* retinoic acid, 9-*cis* retinoic acid, and salts and esters thereof.

The alkylamine is suitably a charged or uncharged secondary, tertiary or quaternary amine, having alkyl groups of 2 to 8 carbon atoms. Specific examples of suitable alkylamines include trioctylamine, triethylamine, spermine and tetrabutylammonium bromide.

This solution is packaged in an inhaler effective to provide a metered dosage of from 50 to 500 μg, preferably about 100 μg, of retinoid per inhalation as shown generally in Fig. 2. Such an inhaler is a combination of a container 1 and a dispenser assembly 2. The dispenser assembly 2 is an open tubular construction which has an actuator portion 3 for receiving the container 1, an oral tube 4 through which the retinoid is dispensed, and an actuator seat 5 which interacts with a metering valve 6 of the container 1. When the

container 1 is pressed downwards within the actuator portion 3, the actuator seat 5 opens the metering valve 6, releasing a dose of retinoid 7 from the container 1, through an orifice 8 in the actuator seat 5 and out through the oral tube 4. A suitable inhaler is a Nasacort® metered dose container. Additional propellant material, for example butane, may be included within the inhaler.

The inhaler is used to administer retinoids directly to the lungs of a patient at risk of epithelial cancer of the respiratory tract. Patients in this category can be identified by behavioral characteristics. For example, individuals who are heavy smokers can be categorized as being at high-risk. Alternatively, a more quantitative approach may be used. Thus, the capacity to metabolize a small test dose of all-trans retinoic acid can be used as an indicator of risk, as described in US Patent Application No. 07/885,130 filed May 18, 1992, which is incorporated herein by reference.

The inhaler provides dosages of from 50 to 500 μg of retinoid per inhalation and is suitably used 1 to 5 times per treatment, with the treatment being repeated 1 to 3 times per day.

A further format which can be used in accordance with the invention to administer an air-borne composition comprising a retinoid to an individual involves the use of a dry powder carrier. Suitable carriers include those which are known to be useful in dry powder inhaler compositions especially the mono-saccharides such as fructose, mannitol, arabinose, xylitol and dextrose (glucose) and their monohydrates, disaccharides such as lactose maltose or sucrose and polysaccharides such as starches, dextrins or dextrans. Retinoids can be formulated into a dry powder with these carrier materials by coating the retinoid onto the surface of the carrier in a micronizer as described generally in US Patent No. 5,376,386 which is incorporated herein by reference. Dry powders containing retinoids are dispensed using known dry powder inhalers in amounts effective to provide dosages comparable to the solubilized formulations discussed above.

EXAMPLE 1

The solubility of all-trans retinoic acid in various solvents was tested as shown in Table 1. Maximum solubility was determined by weighing the residue remaining after evaporation of the solvent.

TABLE 1	
Solvent	Maximum Solubility
ethyl acetate	10 mg/ml
methylene chloride	5 mg/ml
HCFC-123	~2 mg/ml

EXAMPLE 2

To test the ability of alkylamines to enhance the solubility of all-*trans* retinoic acid in chlorofluorocarbons, solutions of the retinoids in various solvents with various amounts of amine stabilizers were prepared as shown in Table 2.

TABLE 2		
Solvent	AlkylAmine - (mg/ml)	Maximum Solubility (mg/ml)
HCFC-123	0	~2
HCFC-123	1.44	~17
HCFC-123	7.22	~44

EXAMPLE 3

To evaluate the bioavailability of retinoids delivered by inhalation, 100 µL of an aqueous solution containing 100 µg of all-*trans* retinoic acid was administered via intratracheal instillation to 3 Sprague-Dawley rats, each weighing approximately 200 g. One rat was then sacrificed at three time points: 1, 6 and 24 hours after treatment. At the time of sacrifice, the chest cavity was opened, both lungs and trachea were removed en bloc, and the right and left lungs were separated by dissection. The liver was also removed, along with a sample of blood obtained by cardia puncture. The blood sample was separated by centrifugation, and plasma plus each of the aforementioned tissues were frozen for later analysis. Subsequently, the tissue was homogenized, and the homogenized

tissue and plasma were extracted with ethanol. The retinoid content was assayed by HPLC, and the results shown in Table 3 were obtained.

TABLE 3 - Tissue /Plasma Concentrations of Retinoic Acid After Intratracheal Instillation (ng/g or tissue or ng/ml of plasma)

Hours	Trachea	Left Lung	Right Lung	Plasma	Liver
1	2859	928	773	123	233
6	96	56	91	ND	24
24	30	22	21	178	23

The results show that this approach provides high levels of retinoid locally, but does not lead to high systemic levels.

EXAMPLE 4

Anesthetized (i.p. pentobarbitol 50 mg/kg) male Sprague-Dawley rates weighing 300 to 700 grams were treated by adminstration of all-*trans* retinoic acid by inhalation, iv injection or intratracheal injection. Inhaled and intratracheal injections were given through an endotracheal tube placed under direct vision over a guidewire as described by Weksler et al., *J. Appl. Physiol.* 76: 1823-1825 (1994). IV doeses were given by catheter injection via the right external jugular vein.

For inhalation, all-*trans* retinoic acid was solublized in hydrofluorocarbon 123 using tetramethylammonium hydroxide and combined with hydrofluoroalkane 134a as propellant. 21 grams of this solutions was packaged in a multdose inhaler that delivered 80 to 120 μg of all-*trans* retinoic acid per dose. When sprayed through the endotracheal tube, this canister supplied 49 μg/dose. However, not all of this dose was absorbed by the rats due to escape through the nasal passages and back through the trachea. Total absorption amounted to 1-2% of the intended 250 μg dose.

For injection, an aqueous solution of all-*trans* retinoic acid was prepared in 20% ethanol; 10% Tween 20; 1mM NH_4OH.

Animals were grouped into three experimental groups and two control groups. The control groups received no treatment or a control inhalant containing no all-*trans* retinoic acid. Animals in the groups receiving iv or intratracheal injections each received a single dose containing 250 μg all-*trans* retinoic acid. Animals in the group treated with the multidose inhaler each received three doses for a total of 147 μg of all-*trans* retinoic acid.

Animals were sacrificed at 5 minutes and at 1, 2, 4 and 6 hours, and blood and tissue was harvested for analysis by HPLC and histology. In addition, animals receiving the inhalant were sacrificed at 24 hours post-treatment.

Figs. 3A and 3B shows the levels of all-*trans* retinoic acid found in the plasma and livers of animals in each of the three treatment groups. As shown, intratracheal injection and aerosol inhalation result in much lower levels of the compound in the liver. On the other hand, as shown in Fig. 4, all three treatments resulted in prolonged levels of all-*trans* retinoic acid in the lungs where it is desired for therapeutic efficacy. Clearance data from plasma and lung tissue is summarized in Table 4.

TABLE 4

Administration Route	Lung t ½ (hours)	Lung AUC (ng-hr/gm)	Plasma t ½ (hours)	Plasma AUC (ng-hr/ml)
iv inj.	1.9	11910	0.9	1385
tracheal inj.	17.7	26972	1.9	191
aerosol inhaler	5.4	262	3	171

As shown, the aerosol inhalation provided sustained levels of all-*trans* retinoic acid in the lungs with lower levels in the plasma compared to iv injections, thus offering the ability to use all-*trans* retinoic acid as a therapeutic agent with a reduction in systemic toxicity. Further, the tracheal injection provides a better model given the limitations of the rat as a recipient of aerosol therapy to assess the utility of such therapy in larger organism, including humans.

CLAIMS

1. A solution comprising

a retinoid,

a chlorofluorocarbon solvent, and

an alkylamine which is effective to solubilize the retinoid in the chlorofluorocarbon solvent.

2. The solution of claim 1, wherein the solution comprises from 0.1 to 5 mg of the retinoid and from 0.1 to 5 mg of the alkylamine per ml of solution.

3. The solution of claim 2, wherein the solution comprises from 1 to 2 mg of the retinoid and 0.1 to 0.5 mg of the alkylamine per ml of solution.

4. The solution of any of claims 1 to 3, wherein the retinoid is all-*trans* retinoic acid.

5. The solution of any of claims 1 to 4, wherein the alkylamine is a secondary, tertiary or quaternary alkylamine having alkyl groups containing from 2 to 8 carbon atoms.

6. The solution of any of claims 1 to 5, wherein the alkylamine is selected from the group consisting of trioctylamine, triethylamine, spermine and tetrabutylammonium bromide.

7. A method for prevention of epithelial cancer of the respiratory tract in an at-risk individual, comprising administering by inhalation to the respiratory tract of the individual an air-borne composition comprising a therapeutically effective amount of at least one retinoid.

8. The method of claim 7, wherein the retinoid is administered in a solution comprising

a retinoid.

a chlorofluorocarbon solvent. and

an amine which is effective to solubilize the retinoid in the chlorofluorocarbon solvent.

9. The method of claim 8, wherein the solution comprises from 0.1 to 10 mg of the retinoid and from 0.1 to 5 mg of the alkylamine per ml of solution.

10. The method of claim 9, wherein the solution comprises from 1 to 2 mg of the retinoid and 0.1 to 0.5 mg of the alkylamine per ml of solution.

11. The method of any of claims 8 to 10 wherein the retinoid is all-*trans* retinoic acid.

12. The method of any of claims 8 to 11, wherein the alkylamine is a secondary, tertiary or quaternary alkylamine having alkyl groups containing from 2 to 8 carbon atoms.

13. The method of any of claims 8 to 12, wherein the alkylamine is selected from the group consisting of trioctylamine, triethylamine, spermine and tetrabutylammonium bromide.

14. An inhaler comprising

(a) a body member containing a reservoir for pharmaceutically-active substance;

(b) a composition disposed within the reservoir, said composition comprising at least one retinoid and a carrier suitable for dispensing from the inhaler; and

(c) means for dispensing a metered dose of the composition from the inhaler.

15. The inhaler of claim 14, wherein the composition is a solution comprising

a retinoid,

a chlorofluorocarbon solvent, and

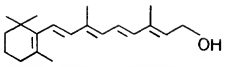
an alkylamine which is effective to solubilize the retinoid in the chlorofluorocarbon solvent.

16. The inhaler of claim 15, wherein the comprises from 0.1 to 10 mg of the retinoid and from 0.1 to 5 mg of the alkylamine per ml of solution.

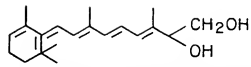
17. The inhaler of claim 16, wherein the solution comprises from 1 to 2 mg of the retinoid and 0.1 to 0.5 mg of the alkylamine per ml of solution.

18. The inhaler of any of claims 15 to 17, wherein the retinoid is all-*trans* retinoic acid.

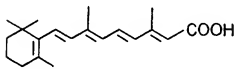
19. The inhaler of any of claims 15 to 18, wherein the alkylamine is a secondary, tertiary or quaternary alkylamine having alkyl groups containing from 2 to 8 carbon atoms.



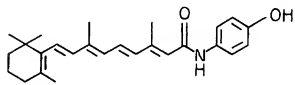
ALL-TRANS RETINOL



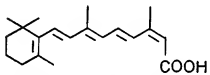
14-HYDROXY-RETRO-RETINOL



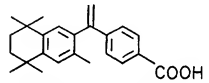
ALL-TRANS RETINOIC ACID



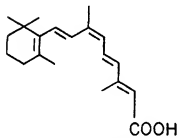
N-(4-HYDROXYPHENYL) RETINAMIDE



13-CIS RETINOIC ACID



3-METHYL TTNEB



9-CIS RETINOIC ACID

FIG. 1

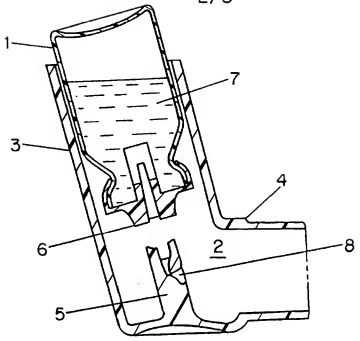
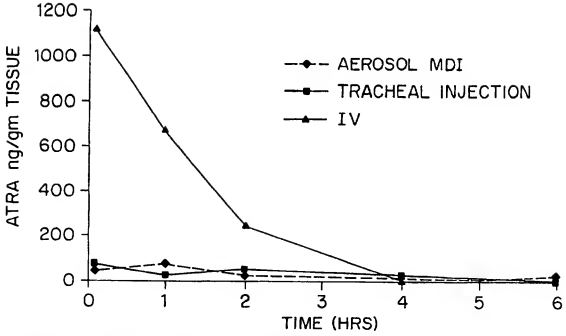
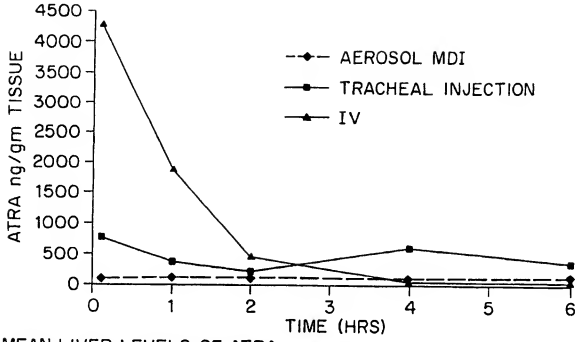


FIG. 2



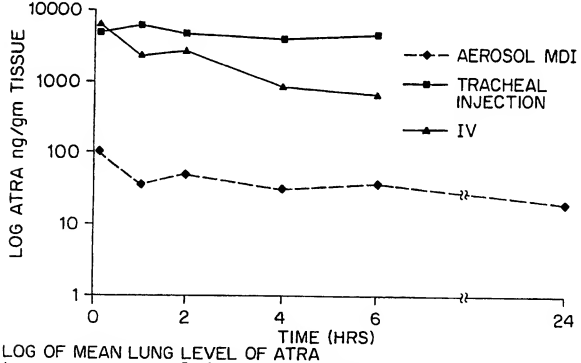
MEAN PLASMA LEVELS OF ATRA (n=3–5 TIME POINT [TP]), IV (n=5/TP), OR INTRA-TRACHEAL INJECTION (n=3/TP).

FIG. 3A



MEAN LIVER LEVELS OF ATRA (n=3-5/TIME POINT[TP]), IV (n=5/TP), OR INTRA-TRACHEAL INJECTION (n=3/TP).

FIG. 3B



LOG OF MEAN LUNG LEVEL OF ATRA (n=3-5/TIME POINT [TP]), IV (n=5/TP), OR INTRA-TRACHEAL INJECTION (n=3/TP). THERE IS NO DATA FOR THE INTRA-TRACHEAL OR IV DOSED ANIMALS AT 24 HRS.

FIG. 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/05409

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/045, 31/165, 31/19
US CL :514/557, 569, 613, 729, 958
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/557, 569, 613, 729, 958

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4,529,600 A (DAWSON ET AL.) 16 June 1985, column 1, lines 30-55 and column 5, line 39 to column 6, line 14.	1-19

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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